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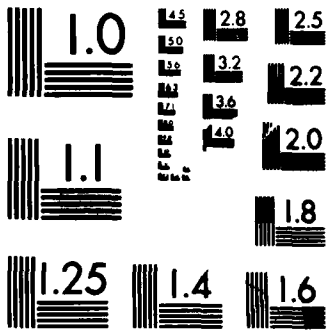

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(U) Development of Synthetic Catalysts for Peptide Bond Cleavage Synthesis and Complete Kinetic Analysis of Compounds 6A, 7A, 8A

12 PERSONAL AUTHOR(S)
Mertes, Kristin Bowman, P.I., Mertes, Mathias Peter, Co-P.I.

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08			Enzyme mimics; Supramolecular; Carboxypeptidase A; Polyammonium macrocycles

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Synthetic mimics for carboxypeptidase A will be synthesized and the structural and chemical factors responsible for catalytic peptidase activity will be probed. Ditopic macrocyclic receptors have been designed which incorporate the salient features of the enzyme analog, namely high affinity complex formation, general base and general acid catalysis, and covalent catalysis. Once synthesized the resulting macrocycle-metal ion complexes should non-specifically promote the hydrolysis of C-terminal peptide bonds. The initial macrocycles will have several types of coordination sites: nitrogen-containing heterocycles, ammonium and ether oxygens. One side of the ditopic receptor will preferentially bind zinc(II) ion, the other the peptide substrate.

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K. B. Mertes
N00014-86-K-0862

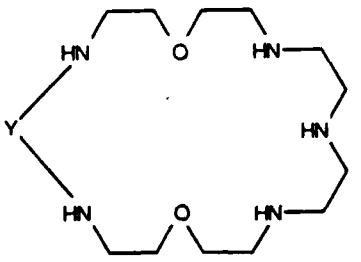
ANNUAL REPORT (YEAR 1)

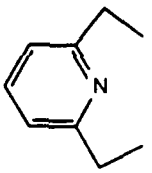
TITLE: Development of Synthetic Catalysts for Peptide Bond Cleavage (Synthesis and Complete Kinetic Analysis of Compounds 6A, 7A, 8A)

REPORT PERIOD: 6 August 1986 to 5 August 1987

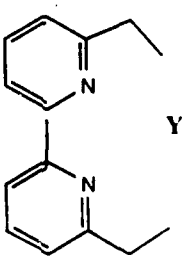
PROJECT GOALS:

The synthesis of ditopic receptors 6A, 7A, and 8A, designed by considering the important interactive features of carboxypeptidase A (CPA) is the goal of this project. Three basic macrocyclic ligands with site specificity for zinc(II) incorporation and functionalized podando groups for covalent catalysis are being synthesized and will be examined for hydrolase activity. The design of the macrocycles allows for a critical assessment of the importance of the interactive sites within the natural enzyme, from the general acid catalysis provided by arginine and tyrosine residues and the zinc(II) ion to the general base or nucleophilic role of the Glu-270 carboxylate residue.

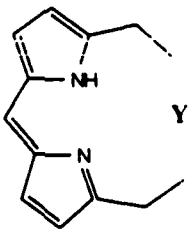




Y = 6A



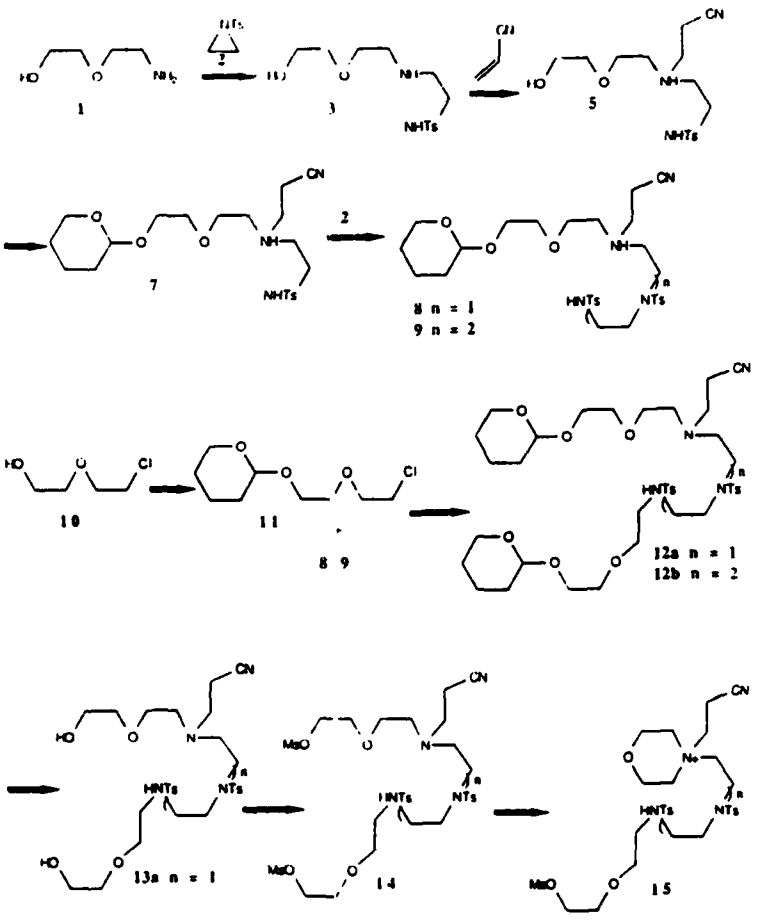
Y = 7A



Y = 8A

ACCOMPLISHMENTS:

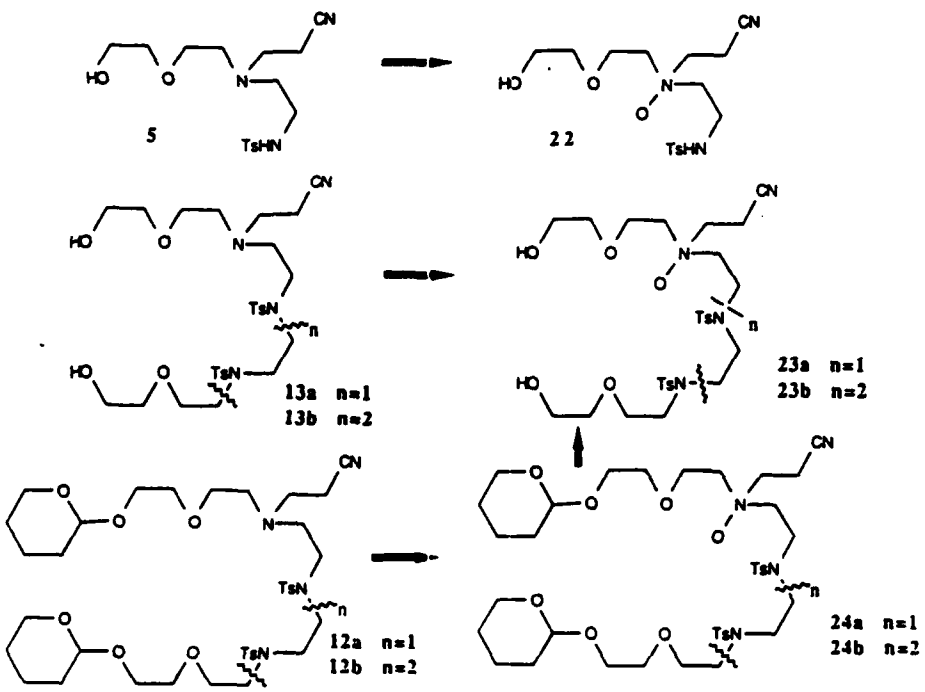
(1) Two pathways have been attempted to synthesize the "eastern" half of the molecule (Schemes 1- 3):



Scheme 1

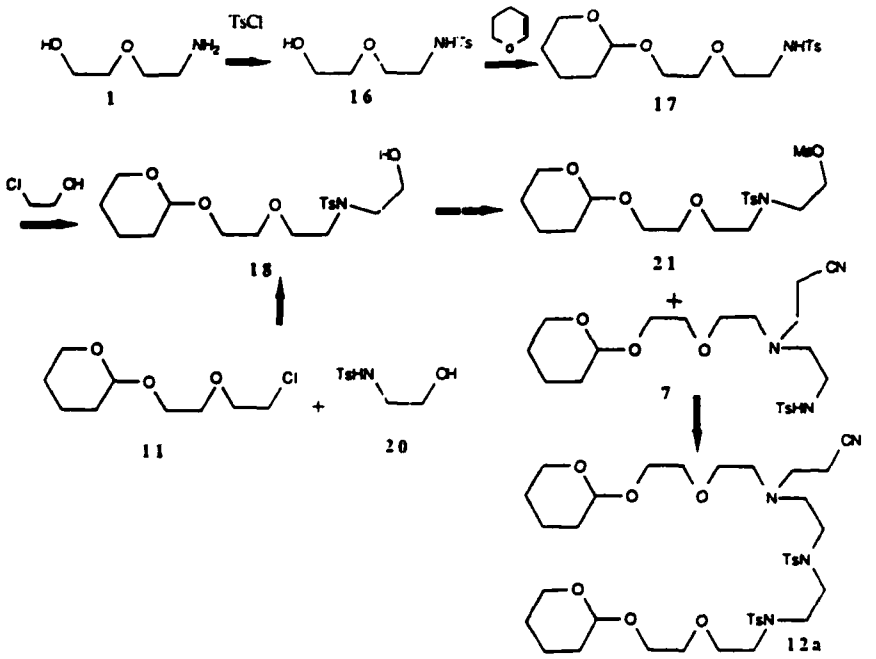
(a) In the Scheme 1 pathway two major synthetic problems have been encountered. In proceeding from 7 to 8 the tosyl aziridine reacts further with the triamine product to give a tetraamine and even higher analogs. Product purification by separation of the diamine reactant and higher polyamine products from the desired triamine has been difficult by traditional column chromatographic techniques. The reactant diamine and product triamine have almost identical retention times in all of the solvent combinations tested. Hence, the isolated desired product always contains a slight amount of undesired contaminant amines.

A second problem was encountered in the mesylation of 13a. During the purification procedure, the desired product 14 was lost due to the undesired ring closure leading to 15. In order to circumvent this problem the nitroso derivative has been synthesized according to Scheme 2. It is readily obtained from either 13a or 12a. Once the macrocycle is formed, established deprotection procedures will be used.



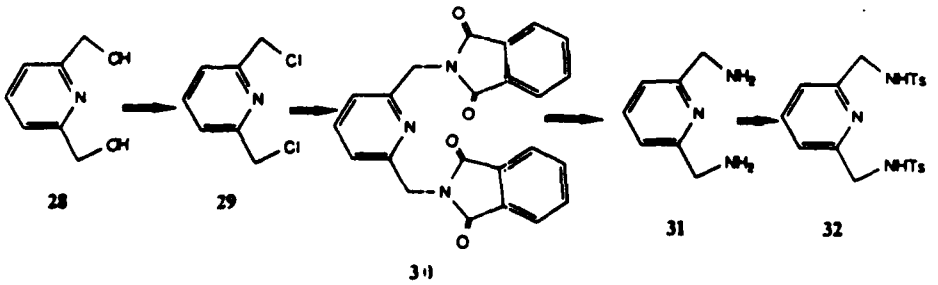
Scheme 2

(b) More recently a convergent synthesis of the "eastern" half is being attempted (Scheme 3). This route circumvents the problem of the higher amine analogs of Scheme 1.

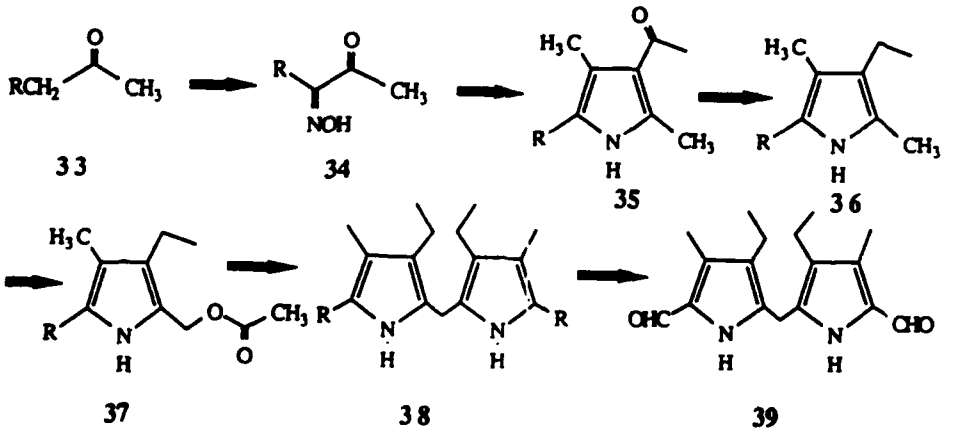


Scheme 3

(2) The "western" halves of 6A and 8A have been synthesized according to the following routes using established procedures (Schemes 4 and 5):



Scheme 4



Scheme 5

PLANS FOR NEXT YEAR:

(1) It is anticipated that the "eastern" half of the macrocycle for formation of 6A will be obtained shortly. Compound 6A will then be synthesized from compounds 14 or the N-protected form of 14 and 32.

(2) Testing will begin immediately on compound 6A using o-(trans-p-chlorocinnamoyl)-L-β-phenyllactate. It is crucial to the remaining compounds to be tested that an initial evaluation of hydrolase activity be obtained as early as possible.

(3) The "western" half of 7A will be synthesized.

(4) Compounds 7A and 8A will be synthesized.

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